

## AMENDMENT AND RESPONSE UNDER 37 CFR § 1.111

Serial Number: 09/732,241

Filing Date: December 7, 2000

Title: THERAPEUTIC CARBAMATES

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Dkt: P-095-RIN THE CLAIMS

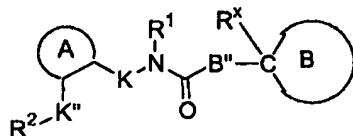
Please amend the claims as follows:

Please cancel claims 27 and 35.

1. (Currently Amended) A compound of Formula (I):



wherein:

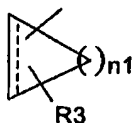
 $L_1$  is a group of formula (a):

(a)

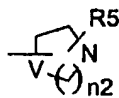
wherein:

 $A$  is an aryl or a heteroaryl ring; $B''$  is  $-O-$ ;

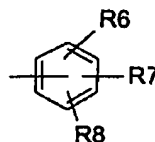
$R^x$  is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, acylamino, aminoacyloxy, aryl, carboxyalkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, heteroaralkyl, alkylsulfonyl, or alkylsulfinyl;

 $R^1$  is hydrogen or alkyl; $R^2$  is Het, or is selected from a group consisting of formula (i), (ii), and (iii):

(i)



(ii)



(iii)

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wherein:

---- is an optional double bond;

 $n_1$  is an integer of from 1 to 4; $n_2$  is an integer of from 1 to 3;V is -CH-, -O-, -S(O) $n_3$ - (where  $n_3$  is an integer of from 0 to 2), or -NR<sup>4</sup>- (wherein R<sup>4</sup> is hydrogen, alkyl, substituted alkyl, aryl, or heteroaryl);"Het" is a heteroaryl ring which optionally attaches a group of formula (a) to a linker;R<sup>3</sup> is hydrogen, alkyl, halo, amino, substituted amino, -OR<sup>a</sup> (where R<sup>a</sup> is hydrogen, alkyl, or acyl), or a covalent bond attaching a group of formula (a) to a linker;R<sup>5</sup> is hydrogen, alkyl, halo, amino, substituted amino, -OR<sup>b</sup> (where R<sup>b</sup> is hydrogen or alkyl), aryl, aralkyl, heteroaralkyl, or a covalent bond attaching a group of formula (a) to a linker;R<sup>6</sup>, R<sup>7</sup>, and R<sup>8</sup> are, independently of each other, hydrogen, halo, hydroxy, alkoxy, haloalkoxy, carboxy, alkoxycarbonyl, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, substituted amino, or a covalent bond attaching a group of formula (a) to a linker;

K is a bond or an alkylene group;

K" is a bond, -C(O)-, -S(O) $n_4$ - (where  $n_4$  is an integer of from 0 to 2), or an alkylene group optionally substituted with a hydroxyl group; andB is heterocycloamino or heteroarylamino, which optionally attaches a group of formula (a) to a linker;provided that at least one of the R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, "Het", heterocycloamino, or heteroarylamino groups attaches a group of formula (a) to a linker;~~X~~ is a linker; andL<sub>2</sub> is an organic group comprising at least one primary, secondary or tertiary amine; andX is a linker of formula:wherein

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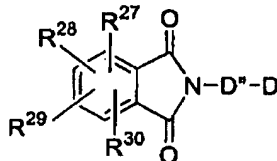
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Dkt. P-095-Rm is an integer of from 0 to 20;X<sup>a</sup> at each separate occurrence is selected from the group consisting of-O-, -S-, -NR-, -C(O)-, -C(O)O-, -C(O)NR-, -C(S)-, -C(S)O-, -C(S)NR- or a covalent bond where R is as defined below;Z at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, and a covalent bond; andY<sup>a</sup> and Y<sup>b</sup> at each separate occurrence are selected from the group consisting of -O-, -C(O)-, -OC(O)-, -C(O)O-, -NR-, -S(O)<sub>n</sub>-, -C(O)NR'-, -NR' C(O)-, -NR' C(O)NR'-, -NR' C(S)NR'-, -C(=NR')-NR'-, -NR'-C(=NR')-, -OC(O)-NR'-, -NR'-C(O)-O-, -P(O)(OR')-O-, -O-P(O)(OR')-, -S(O)<sub>n</sub>CR'R''-, -S(O)<sub>n</sub>-NR'-, -NR'-S(O)<sub>n</sub>-, -S-S-, and a covalent bond; where n is 0, 1 or 2; and R, R' and R'' at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic; provided at least one of X<sup>a</sup>, Y<sup>a</sup>, Y<sup>b</sup> or Z is not a covalent bond;

or a pharmaceutically acceptable salt; or prodrug thereof.

2. (Currently Amended) The compound of claim 1 wherein L<sub>2</sub> is a group selected from a group consisting of:

- (i) a group of formula (b):



(b)

wherein:

D'' is alkylene;

D is -NR<sup>31</sup>R<sup>32</sup>, -N<sup>+</sup>(R<sup>33</sup>R<sup>34</sup>R<sup>35</sup>) or -OR<sup>32</sup> where R<sup>31</sup>, R<sup>33</sup>, and R<sup>34</sup> are, independently of each

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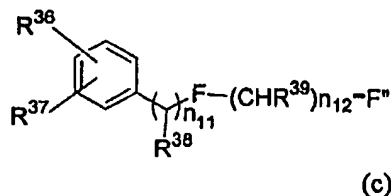
other, hydrogen, alkyl, or aralkyl; and  $R^{32}$  and  $R^{35}$  represent a covalent bond attaching a group of formula (b) to a linker;

$R^{27}$  is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

$R^{28}$  is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, or alkyl optionally substituted with one, two, or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

$R^{29}$  and  $R^{30}$  are, independently of each other, hydrogen, alkyl, haloalkyl, halo, nitro, cyano, hydroxy, alkoxy, alkoxycarbonyl, acyl, thio, alkylthio, amino, mono- or dialkylamino; or one of  $R^{27}$ ,  $R^{28}$ ,  $R^{29}$ , or  $R^{30}$  together with the adjacent group forms a methylenedioxy or ethylenedioxy group;

(ii) a group of formula (c):



wherein:

$n_{11}$  is an integer of from 1 to 7;

$n_{12}$  is 0 to 7;

F is  $-NR^{40}-$ ,  $-O-$ ,  $-S-$ , or  $-CHR^{41}-$  (wherein  $R^{40}$  and  $R^{41}$  are, independently of each other, hydrogen, alkyl, or substituted alkyl);

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F'' is a covalent bond, -OR<sup>43</sup>, -NR<sup>42</sup>R<sup>43</sup>, or -N<sup>+</sup>R<sup>43</sup>R<sup>44</sup>R<sup>45</sup> wherein R<sup>42</sup> is hydrogen or alkyl, R<sup>44</sup> and R<sup>45</sup> are alkyl, and R<sup>43</sup> is hydrogen, alkyl, or a covalent bond attaching a group of formula (c) to a linker;

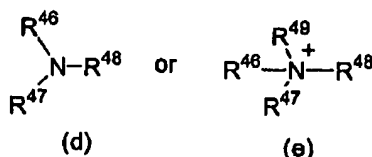
R<sup>36</sup> is hydrogen, alkyl, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

R<sup>37</sup> is hydrogen, alkyl, halo, nitro, cyano, hydroxy, alkoxy, alkoxycarbonyl, acyl, thio, alkylthio, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino; and

R<sup>38</sup> is hydrogen, alkyl, halo, hydroxy, alkoxy, or a covalent bond attaching the ligand to a linker provided that at least one of R<sup>38</sup> and R<sup>43</sup> attaches a group of formula (c) to a linker;

R<sup>39</sup> is hydrogen, alkyl, halo, hydroxy, alkoxy, or substituted alkyl; and

(iii) a group of formula (d) or (e):



wherein:

R<sup>46</sup> is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, or heterocycle;

R<sup>47</sup> is alkyl, substituted alkyl, aryl, acyl, heterocycle, or -COOR<sup>50</sup> where R<sup>50</sup> is alkyl; or

R<sup>46</sup> and R<sup>47</sup> together with the nitrogen atom to which they are attached form a heterocycle, which heterocycle is optionally substituted with one or more alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, cycloalkyl,

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substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl or -SO<sub>2</sub>-heteroaryl;

R<sup>48</sup> is a covalent bond that attaches ~~[[the]]~~ a group of formula (d) to a linker; and

R<sup>49</sup> is alkyl;

or a pharmaceutically acceptable salt; or prodrug thereof.

3. (Original) The compound of claim 1 or 2 wherein A is phenyl or pyridyl.
4. (Original) The compound of claim 1 or 2 wherein R<sup>1</sup> is hydrogen, methyl, or ethyl.
5. (Withdrawn) The compound of claim 1 or 2 wherein R<sup>2</sup> is pyrrolyl, pyridinyl, or imidazolyl.
6. (Original) The compound of claim 1 or 2 wherein R<sup>2</sup> is phenyl.
7. (Original) The compound of claim 1 or 2 wherein K is a bond or a methylene group.
8. (Original) The compound of claim 1 or 2 wherein K" is a bond.
9. (Original) The compound of claim 1 or 2 wherein R<sup>x</sup> is alkyl, alkenyl, or alkynyl, each optionally substituted with 1 to 5 alkoxy or fluoro substituents.
10. (Original) The compound of claim 1 or 2 wherein R<sup>x</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, each optionally substituted with 1 to 3 methoxy, ethoxy or fluoro substituents.

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11. (Original) The compound of claim 1 or 2 wherein R<sup>x</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 to 3 methoxy, ethoxy, or fluoro substituents.
12. (Original) The compound of claim 1 wherein R<sup>x</sup> is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or secbutyl, optionally substituted with methoxy or ethoxy or with 1 to 3 or fluoro substituents.
13. (Original) The compound of claim 1 wherein R<sup>x</sup> is methyl, ethyl, methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxymethyl, formyl, or acetyl.
14. (Original) The compound of claim 1 or 2 wherein R<sup>x</sup> is methyl, ethyl, methoxymethyl, fluoromethyl, difluoromethyl, or trifluoromethyl.
15. (Currently Amended) The compound of claim 1 or 2 wherein B is a heterocycloamino group which attaches a group of formula (a) to a linker.
16. (Currently Amended) The compound of claim 1 or 2 wherein B is pyrrolidine, piperidine, or hexahydroazepine attaching a group of formula (a) to a linker.
17. (Currently Amended) The compound of claim 1 or 2 wherein B is piperidine wherein the nitrogen atom of said piperidine attaches a group of formula (a) to a linker.
18. (Currently Amended) The compound of claim 1 or 2 wherein B is piperidin-3-yl or piperidin-4-yl wherein the nitrogen at the 1 position optionally attaches a group of formula (a) to a linker.
19. (Withdrawn) The compound of claim 1 wherein B taken together with R<sup>x</sup> is 4-methylpiperidine-1,4-diyl.

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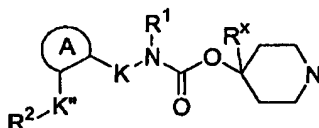
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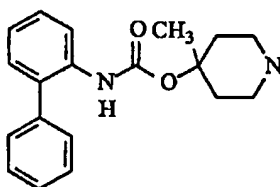
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20. (Withdrawn) The compound of claim 2 wherein  $L_2$  is a group of formula (d) or (e).
21. (Withdrawn) The compound of claim 20 wherein:  $R^{46}$  is alkyl or substituted alkyl;  $R^{47}$  is alkyl, substituted alkyl, or heterocycle; or  $R^{46}$  and  $R^{47}$  together with the nitrogen atom to which they are attached form a heterocycle.
22. (Withdrawn) The compound of claim 1 or 2 wherein  $L_2$  has any one of the formulas A1-A590 in Table 1.
23. (Withdrawn) The compound of claim 1 or 2 wherein  $L_1$  is:



24. (Original) The compound of claim 23 wherein  $L_1$  is:



25. (Original) The compound of claim 24 wherein the piperidino nitrogen of  $L_1$  is bonded to  $X$ .
26. (Withdrawn) The compound of claim 1 or 2 wherein  $X$  is alkylene optionally substituted



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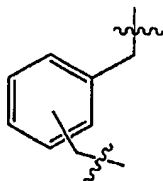
with one, two, or three hydroxy groups, alkylene wherein one, two, or three carbon atoms have been replaced by an oxygen atom, or an -alkylene-phenylene-alkylene- wherein the phenylene ring is optionally substituted with one or two chloro or fluoro groups.

27. (Cancelled)

28. (Withdrawn) The compound of claim 1 or 2 wherein X is an alkylene group having from 3 to 20 carbon atoms; wherein one or more carbon atoms in the alkylene group is optionally replaced with -O-; and wherein the chain is optionally substituted on carbon with one or more hydroxyl.

29. (Withdrawn) The compound of claim 1 or 2 wherein X is nonane-1,9-diyl, octane-1,8-diyl, propane-1,3-diyl, 2-hydroxypropane-1,3-diyl, or 5-oxa-nonane-1,9-diyl.

30. (Withdrawn) The compound of claim 1 or 2 wherein X has the following formula:



wherein the phenyl ring is optionally substituted with 1, 2, or 3 fluoro groups.

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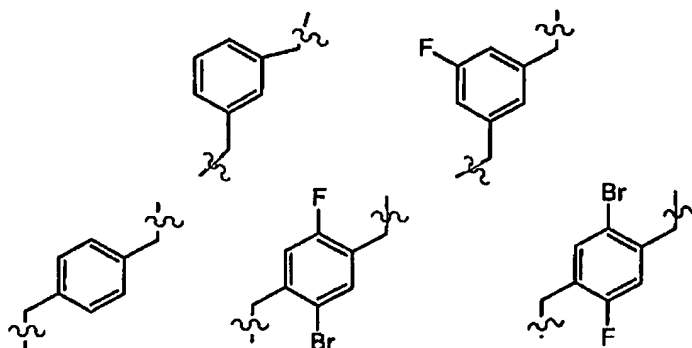
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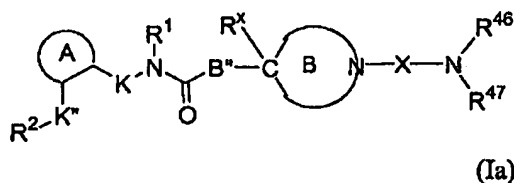
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31. (Withdrawn) The compound of claim 1 or 2 wherein X has one of the following formulas:



32. (Withdrawn) The compound of claim 2 which is a compound of Formula (Ia):



or a pharmaceutically acceptable salt or prodrug thereof.

33. (Withdrawn) The compound of claim 1 or 2 wherein L<sub>2</sub> is a group of formula A234, A363, A364, A153, A28, A324, A329, A562, A87, or A239 in Table 1.

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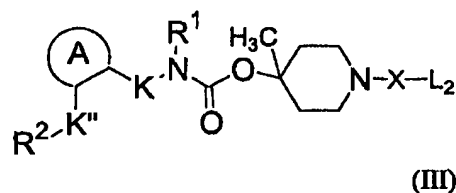
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34. (Withdrawn) The compound of claim 1 which is a compound of formula (III):



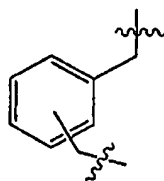
wherein  $R^2$ ,  $K''$ , A, K,  $R^1$ , X, and  $L_2$  have the values defined in claim 1; or a pharmaceutically acceptable salt or prodrug thereof.

35. (Cancelled)

36. (Withdrawn) The compound of claim 34 wherein X is an alkylene group having from 3 to 20 carbon atoms; wherein one or more carbon atoms in the alkylene group is optionally replaced with -O-; and wherein the chain is optionally substituted on carbon with one or more hydroxyl.

37. (Withdrawn) The compound of claim 34 wherein X is nonane-1,9-diyl, octane-1,8-diyl, propane-1,3-diyl, 2-hydroxypropane-1,3-diyl, or 5-oxa-nonane-1,9-diyl.

38. (Withdrawn) The compound of claim 34 wherein X has the following formula:



wherein the phenyl ring is optionally substituted with 1, 2, or 3 fluoro groups.

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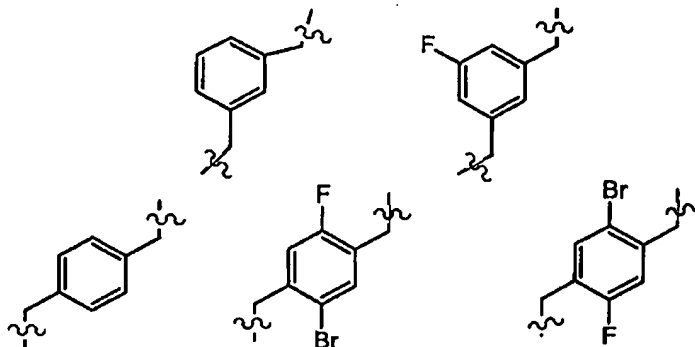
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39. (Withdrawn) The compound of claim 34 wherein X has one of the following formulas:



40. (Withdrawn) The compound of claim 2 wherein  $L_2$  is a group of formula (d) wherein  $R^{46}$  is a heterocycle, optionally substituted with 1 to 5 substituents independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl; and  $R^{47}$  is alkyl, substituted alkyl, acyl, or  $-COOR^{50}$ .

41. (Withdrawn) The compound of claim 2 wherein  $L_2$  is a group of formula (d) wherein  $R^{46}$  is alkyl that is optionally substituted with from 1 to 5 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, aminoacyl, aminoacyloxy, oxyaminoacyl, cyano, halogen, hydroxyl, keto, thioketo, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, and  $NR^aR^b$ , wherein  $R^a$  and  $R^b$  may be the same or different [and] and are chosen from hydrogen, alkyl, substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, and heterocyclic.

42. (Withdrawn) The compound of claim 2 wherein  $L_2$  is a group of formula (d) wherein  $R^{46}$  is 3-piperidinyl, 4-piperidinyl, or 3-pyrrolidinyl, which  $R^{46}$  is optionally substituted with 1 to 3 substituents independently selected from the group consisting of alkoxy, substituted alkoxy,

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cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, cyano, halogen, hydroxyl, keto, thioketo, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl.

43. (Withdrawn) The compound of claim 2 wherein R<sup>46</sup> and R<sup>47</sup> together with the nitrogen atom to which they are attached form a piperidine or pyrrolidine ring which ring is optionally substituted with 1 to 3 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, cyano, halogen, hydroxyl, keto, thioketo, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl.

44. (Withdrawn) The compound of claim 2 wherein R<sup>46</sup> and R<sup>47</sup> together with the nitrogen atom to which they are attached form a heterocycle that is an aza-crown ether.

45. (Withdrawn) The compound of claim 44 wherein the aza-crown ether is 1-aza-12-crown-4, 1-aza-15-crown-5, or 1-aza-18-crown-6.

46. (Withdrawn) Compound number 1-146 as described in Table A and Table B herein, or a pharmaceutically acceptable salt or prodrug thereof.

47. (Original) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 1 or 2.

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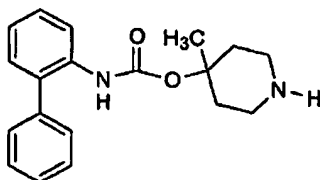
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48. (Original) A method of treating a disease mediated by a muscarinic receptor in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of claim 1 or 2.

49. (Previously Presented) The method of claim 48 wherein the disease is urinary incontinence, chronic pulmonary obstructive disease, asthma, hyper salivation, a cognitive disorder, blurred vision, or irritable bowel syndrome.

50. (Previously Presented) A compound of formula L<sub>1</sub>-H wherein L<sub>1</sub> has the values defined in claim 1; or a salt thereof.

51. (Original) The compound of claim 50 which is a compound of formula (V):



(V)

or a salt thereof.

52. (Withdrawn) A compound of formula R<sub>a</sub>-X-L<sub>2</sub> wherein X and L<sub>2</sub> have the values defined in claim 2; and R<sub>a</sub> is a suitable leaving group.